Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Pd-Catalyzed Alkene Diamination Reactions of Nitrogen Electrophiles: Synthesis of Cyclic Guanidines and Ureas Bearing Dialkylaminomethyl Groups

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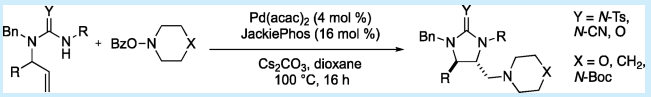
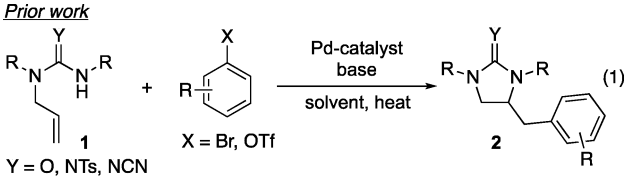
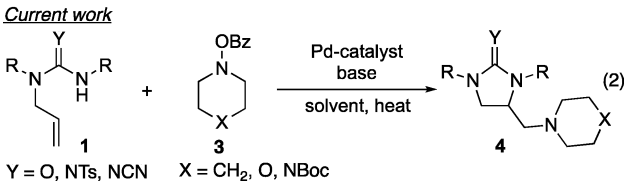
Supporting Information

ABSTRACT: The Pd-catalyzed coupling of *N*-allylguanidines or *N*-allylureas with *O*-benzoylhydroxylamine derivatives affords cyclic guanidines or cyclic ureas bearing dialkylaminomethyl groups. The desired products are obtained in good yield, and substrates bearing substituents at the allylic position are transformed with moderate diastereoselectivity. The mechanism of these reactions appears to involve *anti*-aminopalladation of the alkene, followed by a rare sp^3C-sp^3N bond-forming reductive elimination from an alkylpalladium complex that contains *β*-hydrogen atoms.

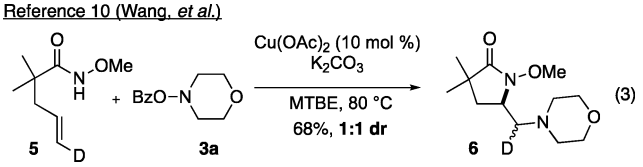


Over the past 14 years, our group has reported a series of Pd-catalyzed alkene difunctionalization reactions between aryl or alkenyl halides or triflates and alkenes bearing pendant nucleophiles.[1] For example, treatment of an *N*-allyl urea or guanidine derivative (**1**) with an aryl halide or triflate affords heterocyclic product **2** in good yield (eq 1).[2] These transformations are effective with a broad range of nucleophiles, the reactions are stereospecific with respect to alkene geometry, and substrates bearing substituents on the alkene or the alkyl tether are generally transformed with good to excellent levels of diastereoselectivity. Despite the utility of these transformations, to date, all reactions have involved the use of carbon-centered electrophiles, which leads to the formation of one C−C bond and one carbon−heteroatom bond during the alkene addition.





In recent years, the use of O-acylated hydroxylamine derivatives as nitrogen-centered electrophiles **3** in metal-catalyzed reactions has attracted considerable attention.[3] We were interested in investigating the utility of these electrophiles in heterocycle-forming alkene diamination reactions[4−6] of substrates such as **1** that are mechanistically related to our Pd-catalyzed alkene carboamination reactions (eq 2). These transformations would provide heterocyclic products bearing an appended dialkylaminomethyl group (**4**), which are subunits displayed in some biologically active compounds.[7] The final step in the alkene diamination catalytic cycle would be an sp^3C-sp^3N bond-forming reductive elimination from an alkylpalladium complex, which is a very rare organometallic transformation,[8] and was expected to be challenging to achieve. However, recent studies on alkane C−H functionalization with these electrophiles suggested that this reductive elimination step may be possible.[8a,9] In addition, although Wang has reported an analogous, Cu-catalyzed alkene diamination reaction involving N-alkoxypentamides or N^1-allyl-N^2-methoxyureas as substrates,[10−12] the Cu-catalyzed reactions reported thus far are not stereospecific, with respect to alkene geometry, because of the radical character of an intermediate alkylcopper complex (eq 3):[10]



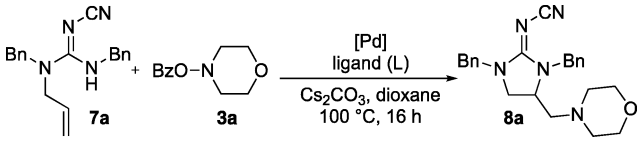
Thus, it appeared that the Pd-catalyzed process could have advantages over the Cu-catalyzed reactions, since our Pd-catalyzed alkene carboamination reactions are stereospecific, and we anticipated that the new diamination reactions would also be stereospecific.

In order to explore the feasibility of Pd-catalyzed alkene diamination reactions involving nitrogen electrophiles, we first examined the coupling of **7a** with morpholino benzoate (**3a**) to afford cyclic guanidine product **8a** (see Table 1). Initially, we employed catalysts derived from $Pd(OAc)_2$ and the ligands DPE-Phos, CPhos, and XantPhos, because these ligands provided good to excellent results in alkene carboamination

Received: April 23, 2018

DOI: 10.1021/acs.orglett.8b01289
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization Studies[a]



entry	[Pd]	ligand (L)	catalyst loading	yield[b] (%)
1	$Pd(OAc)_2$	DPE-Phos	2 mol % [Pd] 4 mol % L	13
2	$Pd(OAc)_2$	CPhos	2 mol % [Pd] 8 mol % L	0
3	$Pd(OAc)_2$	XantPhos	2 mol % [Pd] 8 mol % L	0
4	$Pd(OAc)_2$	$P(C_6F_5)_3$	2 mol % [Pd] 8 mol % L	30
5	$Pd_2(dba)_3$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	0
6	$Pd(TFA)_2$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	40
7	$Pd(acac)_2$	$P(C_6F_5)_3$	4 mol % [Pd] 16 mol % L	60
8	$Pd(acac)_2$	$P[C_6H_3\text{-}3,5\text{-}(CF_3)_2]_3$	4 mol % [Pd] 16 mol % L	80
9	$Pd(acac)_2$	JackiePhos	4 mol % [Pd] 16 mol % L	95
10	**$Pd(acac)_2$**	**JackiePhos**	**4 mol % [Pd] 16 mol % L**	**95**[c]
11	$Pd_2(dba)_3$	JackiePhos	4 mol % [Pd] 16 mol % L	0[c]
12	$Pd(acac)_2$	JackiePhos + dba	4 mol % [Pd] 16 mol % L 6 mol % dba	25[c]
13	G3-JackiePhos	JackiePhos	4 mol % [Pd] 16 mol % L[d]	<5[c]
14	G3-JackiePhos	no added ligand	4 mol % [Pd]	5[c]
15	G3-JackiePhos	JackiePhos + acac	4 mol % [Pd] 16 mol % L[d] 8 mol % acac	35[c]

[a]Conditions: 1.0 equiv **7a**, 4.0 equiv **3a**, 2 equiv Cs_2CO_3, [Pd], ligand (L), dioxane (0.1 M), 100 °C, 16 h. [b]Yields were determined by ^1H NMR using 1,10-phenanthroline as an internal standard. [c]The reaction was conducted using 3 equiv **3a** instead of 4 equiv. [d]The reaction was conducted with 12 mol % added JackiePhos (plus the 4 mol % of JackiePhos bound to the G3 complex).

reactions of **7a** and related nucleophiles.[1,2] No desired product was obtained with the CPhos or XantPhos ligands, but we were gratified to find that the use of DPE-Phos led to the formation of the desired product in a measurable, but low yield.[13] Subsequently, we turned our attention to electron-poor monodentate phosphines, because ligands such as $P(C_6F_5)_3$ have provided good results in other Pd-catalyzed transformations of nitrogen electrophiles,[9a,14] and it seemed that the electron-poor ligand may accelerate the $sp^3C–sp^3N$ bond-forming reductive elimination step.[15] The use of $P(C_6F_5)_3$ as the ligand resulted in an improved 30% yield of **8a**, and after surveying several palladium sources, we found that the use of $Pd(acac)_2$ led to a further increase to 60% yield. The combination of $P[3,5\text{-}(CF_3)_2C_6H_3]_3$ as the ligand and $Pd(acac)_2$ as the precatalyst was even better, with **8a** generated in 80% yield. Finally, we examined the biarylphosphine JackiePhos, which contains two $3,5\text{-}(CF_3)_2C_6H_3$ groups on the phosphorus atom and has previously been shown to promote challenging $sp^2C–N$ bond-forming reductive elimination;[16] we were delighted to obtain a 95% NMR yield of **8a**. With this catalyst system, we were able to decrease the amount of electrophile used from 4 equiv to 3 equiv, but the use of 2 equiv or less of the electrophile resulted in diminished yields.

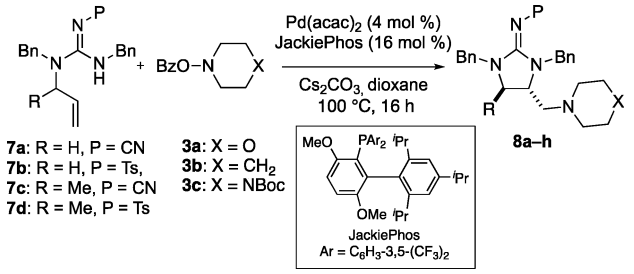
Once the satisfactory conditions were in hand, we conducted a few additional experiments to further examine the influence of precatalyst structure on yield. Although the $Pd(acac)_2$/JackiePhos catalyst system provided excellent results (entry 10 in Table 1), the use of $Pd_2(dba)_3$ as a precatalyst for this reaction completely inhibited product formation (entry 11 in Table 1). The addition of 6 mol % dba to the otherwise optimal conditions (entry 12 in Table 1) resulted in the formation of **8a** in only 25% yield. Use of the Buchwald G3-JackiePhos catalyst precursor in place of $Pd(acac)_2$ failed to produce significant amounts of the desired product (≤5%; see entries 13 and 14 in Table 1). However, when 8 mol % acac (2,4-pentanedione) was added to a reaction in which the G3-JackiePhos complex was used as precatalyst, **8a** was generated in 35% yield. These results indicate that (a) the failure of $Pd_2(dba)_3$ to serve as a viable precatalyst is probably due to inhibition by the dba ligand rather than the zerovalent oxidation state of that complex; and (b) acac plays a key role in these reactions, either by facilitating reactivity of an intermediate along the catalytic cycle or, more likely, by inhibiting catalyst deactivation.

Then, we explored the scope of the Pd-catalyzed coupling reactions of *N*-cyano and *N*-tosylguanidine substrates **7a–7d** with several different electrophiles. As shown in Table 2, these transformations are effective with *O*-benzoylhydroxylamine electrophiles derived from morpholine (**3a**), piperidine (**3b**), and *N*-boc piperazine (**3c**). However, efforts to employ an acyclic electrophile derived from *N*-methyl benzylamine led to the formation of a complex mixture of products. Reactions of substrates **7c–7d** bearing an allylic methyl group proceeded to afford **8f–8h** in good yield and moderate diastereoselectivity (3:1 diastereomeric ratio (dr)). These diastereoselectivities are comparable to those obtained in analogous Pd-catalyzed carboamination reactions of **7c** and **7d** with aryl bromides.[2a] Attempts to employ substrates bearing either 1,1- or 1,2-disubstituted alkenes, thus far, have been unsuccessful.

We also briefly explored the coupling of urea substrates **9a–9c** to afford **10a–10f**. As shown in Table 3, the reactions of **9a** proceeded smoothly with electrophiles derived from morpholine (90% yield on a 0.1 mmol scale and 76% yield on a 1.0 mmol scale) and piperidine (83% yield). However, use of electrophile **3c** derived from *N*-boc piperazine led to a

DOI: 10.1021/acs.orglett.8b01289
Org. Lett. XXXX, XXX, XXX–XXX

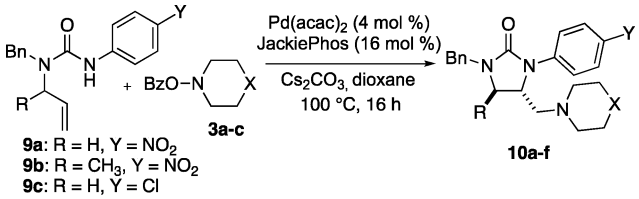
Table 2. Diamination of *N*-Allylguanidines[a]



entry	P	X	R	diastereomeric ratio, dr[b]	yield[c] (%)
1	CN	O	H		91 (**8a**)
2	CN	CH_2	H		92 (**8b**)
3	CN	NBoc	H		61 (**8c**)
4	Ts	O	H		86 (**8d**)
5	Ts	CH_2	H		77 (**8e**)
6	CN	O	Me	3:1 (4:1)	75 (**8f**)
7	CN	CH_2	Me	3:1	81 (**8g**)
8	Ts	O	Me	3:1	88 (**8h**)

[a]Conditions: 1.0 equiv **7**, 3.0 equiv **3**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Diastereomeric ratios were determined by ^1H NMR analysis. Numbers shown in parentheses are dr values for the crude reaction mixture in cases where the crude and isolated dr differed. [c]Isolated yield (average of two or more experiments).

Table 3. Diamination of *N*-Allylureas[a]



entry	Y	X	R	diastereomeric ratio, dr[b]	yield[c] (%)
1	NO_2	O	H		90 (**10a**)
2	NO_2	CH_2	H		83 (**10b**)
3	NO_2	NBoc	H		46 (**10c**)
4	NO_2	O	Me	2:1	32 (**10d**)
5[d]	Cl	O	H		45 (**10e**)
6[d]	Cl	CH_2	H		14 (**10f**)

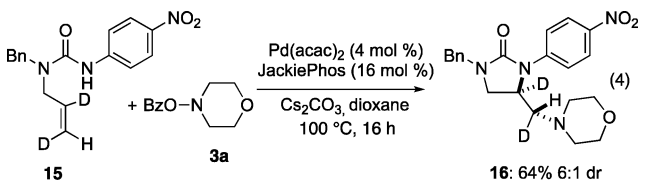
[a]Conditions: 1.0 equiv **9**, 3.0 equiv **3**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Diastereomeric ratios were determined by ^1H NMR analysis. [c]Isolated yield (average of two or more experiments). [d]The reaction was conducted with 4 mol % $Pd(acac)_2$ and 6 mol % JackiePhos.

modest yield of the desired product. Although the presence of a methyl group at the allylic position was well-tolerated in the reactions of guanidine nucleophiles **7c** and **7d** (Table 2, entries 6–8), the coupling of analogous urea substrate **9b** proceeded in low yield (32%) to afford **10d** with 2:1 dr. Use of the substrate **9c**, which contains an *N*-*p*-chlorophenyl group, led to lower yields than were observed in reactions of **9a**, because of competing decomposition of the urea substrate to give *N*-allylbenzylamine.

In order to gain insight into the mechanism and stereospecificity of these new transformations, we examined the reactivity of deuterated substrates ***d*-7a**, ***d*-7b**, and ***d*-9a**. As shown in Table 4, the coupling of ***d*-7a** with **3a** afforded *anti*-addition product ***d*-8a** in 67% yield and 3:1 dr. The reactions of urea substrate ***d*-9a** and *N*-tosylguanidine ***d*-7b** with morpholino benzoate also proceeded via *anti*-addition to the alkene, but with higher diastereoselectivity (6:1 dr in both cases). The coupling of piperidin-1-yl benzoate **3b** with ***d*-7b** gave slightly higher diastereoselectivity (7:1 dr) than was obtained with morpholino benzoate. Thus, in contrast to the related copper-catalyzed diamination reactions,[10] the Pd-catalyzed alkene diamination reactions are stereospecific, although the transfer of stereochemical information from substrate to product is thus far imperfect (but arguably synthetically useful).

Based on the alkene addition stereochemistry, we propose that these new Pd-catalyzed alkene diamination reactions proceed via the catalytic cycle shown in Scheme 1. Initial ligation and reduction of the $Pd(acac)_2$ precatalyst leads to the formation of a Pd(0) complex, which then undergoes oxidative addition to the *O*-benzoyl hydroxylamine **3a** to afford intermediate **11**.[17] Coordination of the alkene to the Pd-complex followed by deprotonation and *anti*-amino-palladation of **12** then affords **13**,[18] which undergoes C–N bond-forming reductive elimination to yield ***d*-10a** with concomitant regeneration of the Pd(0) catalyst. Although we currently favor this proposed mechanism, at this point, we cannot rule out an alternative pathway involving the oxidation of **13** to Pd(IV) complex **14**, followed by reductive elimination to afford the product with the formation of **11** to close the catalytic cycle.

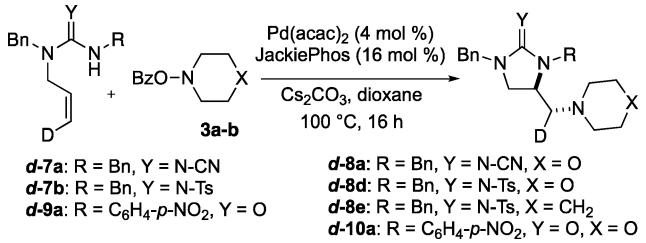
The minor stereoisomer observed in these reactions most likely originates via one of two pathways: (a) competing *syn*-aminopalladation via a palladium bis(amido) complex; or (b) erosion of the stereochemistry of intermediate **13** (or **14**, as the case may be) via β-hydride elimination/reinsertion to generate a tertiary α-amino palladium complex, which can undergo rotation around the C–CH_2D bond followed by a second β-hydride elimination/reinsertion to invert the stereogenic center.[19] In order to probe this question, we sought to slow the rate of potential β-hydride elimination from **13** by replacing the H atom on the internal alkene carbon with a deuterium atom (R = D). We hoped that this substitution would either lead to higher stereocontrol, therefore suggesting that the minor stereoisomer originates from β-hydride elimination,[20] or would lead to no change in stereoselectivity, which would imply that the modest stereocontrol is due to competing *syn*- vs *anti*-aminopalladation.[21] As such, doubly deuterated alkene substrate **15** was prepared and subjected to our standard reaction conditions. As shown in eq 4, this transformation afforded **16** in 64% yield and 6:1 dr, which is comparable to that obtained in the reaction of ***d*-9a**. Thus, the minor stereoisomer appears to result from competing *syn*-aminopalladation.



In conclusion, we have developed a new class of Pd-catalyzed alkene diamination reactions that involve the coupling of *O*-benzoyl hydroxylamine-derived electrophiles with *N*-allylguanidine or urea derivatives. The transformations proceed via stereospecific *anti*-addition of the two N atoms to

DOI: 10.1021/acs.orglett.8b01289
Org. Lett. XXXX, XXX, XXX–XXX

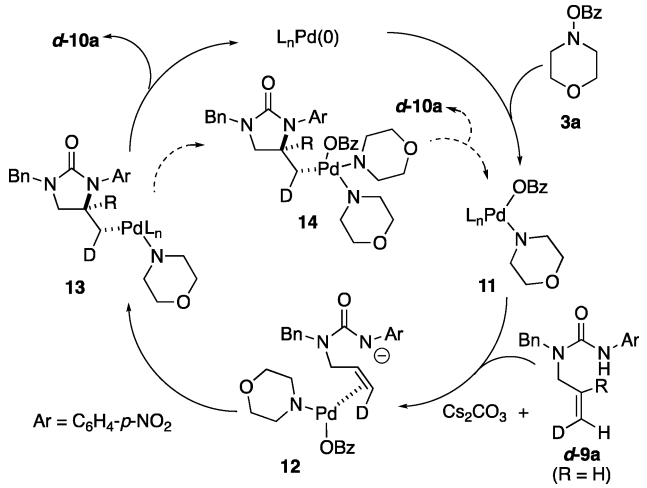
Table 4. Alkene Addition Stereochemistry[a]



entry	Y	R	X	diastereomeric ratio, dr	yield[b] (%)
1	N−CN	Bn	O	3:1	67 (***d*-8a**)
2	O	C_6H_4-*p*-NO_2	O	6:1	75 (***d*-10a**)
3	N−Ts	Bn	O	6:1	75 (***d*-8d**)
4	N−Ts	Bn	CH_2	7:1	77 (***d*-8e**)

[a]Conditions: 1.0 equiv **7a** and **7b** or **9a**, 3.0 equiv **3a** or **3b**, 2 equiv Cs_2CO_3, 4 mol % $Pd(acac)_2$, 16 mol % JackiePhos, dioxane (0.1 M), 100 °C, 16 h. Reactions were conducted on a 0.1 mmol scale. [b]Isolated yield (average of two or more experiments).

Scheme 1. Catalytic Cycle: Working Hypothesis



the alkene with up to 7:1 dr, which is in sharp contrast to previously reported Cu-catalyzed reactions.[10] These transformations appear to proceed via a rare sp^3C-sp^3N bond-forming reductive elimination, which is facilitated by the bulky, electron-poor JackiePhos ligand. Future studies will be directed toward expanding the scope and improving the stereocontrol in these transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01289.

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the University of Michigan for financial support of this work. We also thank Elsa M. Hinds (University of Michigan) for preparation and characterization of substrate **9c**.

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DOI: 10.1021/acs.orglett.8b01289
Org. Lett. XXXX, XXX, XXX−XXX